

**PATENT COOPERATION TREATY**

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
 STEPHANA E. PATTON  
 EDWARDS & ANGELL, LLP  
 P.O BOX 55874  
 BOSTON, MA 02205

**PCT**

RECEIVED  
 19 AUG 24 2005  
 EDWARDS & ANGELL, LLP  
 IP DOCKETING DEPT. (BOS)

**NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT AND  
 THE WRITTEN OPINION OF THE INTERNATIONAL  
 SEARCHING AUTHORITY, OR THE DECLARATION**

(PCT Rule 44.1)

Applicant's or agent's file reference 61198 PCT (47381)	Date of mailing (day/month/year) <b>19 AUG 2005</b>
International application No. PCT/US05/18757	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant SALIX PHARMACEUTICALS INC.	International filing date (day/month/year) 27 May 2005 (27.05.2005)

1.  The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  
 no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US  
 Mail Stop PCT, Attn: ISA/US  
 Commissioner for Patents  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 Facsimile No. (703) 305-3230

Authorized officer  
  
 Christopher Low  
 Telephone No. (703)-872-9306

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

Voluntary Amendment  
 EDWARDS & ANGELL LLP  
 101 Federal St. Boston, MA 02110

Docketed For 9/19/05-10/19/05  
 By Stephanie E. Patton

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 61198 PCT (47381)	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US05/18757	International filing date (day/month/year) 27 May 2005 (27.05.2005)	(Earliest) Priority Date (day/month/year) 28 May 2004 (28.05.2004)
Applicant SALIX PHARMACEUTICALS INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the Report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b.  With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2.  Certain claims were found unsearchable (See Box No. II)

3.  Unity of invention is lacking (See Box No. III)

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b.  none of the figures is to be published with the abstract.

## Box IV TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

The present invention provides a new method of ameliorating and/or treating enteritis induced by radiation therapy, alone or in combination with other therapies, for the treatment of, for example, gastrointestinal malignancies, including colorectal, appendiceal, anal, or small bowel cancers; urogenital malignancies, including prostate, bladder, testicular, or penile cancers; gynecologic malignancies, including cervical, endometrial, ovarian, vaginal, or vulvar cancers; or osteogenic and other sarcomatous malignancies in which pelvic structures are involved, comprising the administration of a therapeutically effective amount of balsalazide to a patient in need thereof.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US05/18757

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 31/16  
US CL : 514/615

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 514/615

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0078205 A1 (PODOLSKY) 24 April 2003 (24.04.2003), see entire document, especially paragraphs [0003], [0005], [0007]-[0009], [0020], [0027], [0080], [0092] and Example 1.	1-8,12-20,25-26
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Y		1-26
X	US 2002/0049186 A1 (EKWURJBE et al) 25 April 2002 (25.04.2002), see entire document, especially paragraphs [0025]-[0033], [0039] and [0059].	1,12
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Y		1-26
A	US 6,197,341 B1 (FRIESS et al) 06 March 2001 (06.03.2001), see entire document.	1-26
A	US 5,498,608 (JOHNSON et al) 12 March 1996 (12.03.1996), see entire document.	1-26

Further documents are listed in the continuation of Box C.

See patent family annex.

•	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

27 July 2005 (27.07.2005)

Date of mailing of the international search report

19 AUG 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Christopher Low

Telephone No. (703)-872-9306

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US05/18757

**10/588254**  
**IAP11 Rec'd PCT/PTO 02 AUG 2006**

**Continuation of B. FIELDS SEARCHED Item 3:**

EAST ONLINE (Search Terms Used: balsalazide, balasalazide, 2-hydroxy-5-phenylazobenzoic acid, 2-hydroxy-5-phenylazobenzoate, colazal, balsalazida, balsalazide, balsalazido, balsalazidum, colazide, radiation, radiotherapy, chemotherapy, cancer, carcinoma, neoplastic, neoplasm, malignant, malignancy, enteritis, radiation induced enteritis, radiation induced injury, intestinal inflammation, radiation enteritis, gastrointestinal, colon, mucosa, mucosal, GI, brachytherapy, intracavitary brachytherapy, interstitial brachytherapy)

STN ONLINE (Databases Used: Registry, Medline, CancerLit, Biosis, Embase, WPIDS; Search Terms Used: same as above)

**PATENT COOPERATION TREATY**

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:  
STEPHANA E. PATTON  
EDWARDS & ANGELL, LLP  
P.O BOX 55874  
BOSTON, MA 02205

**PCT**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

(PCT Rule 43bis.1)

		Date of mailing (day/month/year) <b>19 AUG 2005</b>
Applicant's or agent's file reference  61198 PCT (47381)		<b>FOR FURTHER ACTION</b> See paragraph 2 Below
International application No.  PCT/US05/18757	International filing date (day/month/year)  27 May 2005 (27.05.2005)	Priority date (day/month/year)  28 May 2004 (28.05.2004)
International Patent Classification (IPC) or both national classification and IPC  IPC(7): A61K 31/16 and US Cl.: 514/615		
Applicant  SALIX PHARMACEUTICALS INC.		

**1. This opinion contains indications relating to the following items:**

<input checked="" type="checkbox"/>	Box No. I	Basis of the opinion
<input type="checkbox"/>	Box No. II	Priority
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input type="checkbox"/>	Box No. VIII	Certain observations on the international application

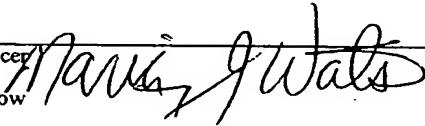
**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

Name and mailing address of the ISA/ US  Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer/ Christopher Low  Telephone No. (703)-872-9306
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Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/18757

**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

This opinion has been established on the basis of a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

a sequence listing

table(s) related to the sequence listing

b. format of material

in written format

in computer readable form

c. time of filing/furnishing

contained in international application as filed.

filed together with the international application in computer readable form.

furnished subsequently to this Authority for the purposes of search.

3.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application  
PCT/US05/18757

10/588254  
IAP11 Rec'd PCT/PTO 02 AUG 2006

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Claims 9-11,21-24

YES

Claims 1-8,12-20,25-26

NO

Inventive step (IS)

Claims NONE

YES

Claims 1-26

NO

Industrial applicability (IA)

Claims 1-26

YES

Claims NONE

NO

2. Citations and explanations:

Claims 9-11 and 21-24 meet the criteria under PCT Article 33(2) for novelty because the prior art fails to teach the presently claimed dosage amounts and regimen of administration of balsalazide for the treatment of radiation induced enteritis.

Claims 1-8, 12-20 and 25-26 do not meet the criteria under PCT Article 33(2) for novelty because the prior art of PODOLSKY (see particularly Example 1) and EKWURIBE et al teach the presently claimed method of treating radiation induced enteritis using a therapeutically effective amount of balsalazide in combination with, respectively, intestinal trefoil peptide or other immunoregulatory compounds of the type disclosed by EKWURIBE et al. PODOLSKY teaches the use of a intestinal trefoil peptide composition in combination with a second therapeutic agent such as balsalazide used for the treatment of proctitis, enteritis and/or mucositis that results from antineoplastic therapy, including both chemotherapy and radiotherapy, particularly when radiotherapy is delivered to the abdomen for the treatment of, for example, colorectal, cervical, uterine, ovarian or prostate cancer. Therapy may be administered within 1, 3, 7 or 14 days following final antineoplastic treatment, concurrently with antineoplastic treatment, 1, 3, 7 or 14 days prior to antineoplastic treatment or continuously (i.e., before, during and after antineoplastic therapy). The teaching of enteritis resulting from antineoplastic radiation treatment is considered to encompass both chronic or acute enteritis conditions.

Claims 1-26 do not meet the criteria under PCT Article 33(3) for inventive step because the prior art of PODOLSKY and EKWURIBE et al teach the presently claimed method of treating radiation induced enteritis or colitis using therapies containing balsalazide. While the references do not expressly teach the presently claimed dosage amounts or regimen of administration, the determination of the optimum dosage amounts and the optimum schedule of administration would have been a matter well within the purview of the skilled artisan. Such a determination would have been made in accordance with a variety of factors, such as the age, sex, weight, overall health of the patient, severity of the disease, tolerability of the therapeutic agent(s), toxicological considerations and pharmacological considerations, such as the rate of absorption, distribution, metabolism and excretion. Thus, the dosage amounts or the dosage regimen that would have been determined by the skilled artisan from the teachings of the prior art of PODOLSKY or EKWURIBE is not expected to differ significantly from what is presently claimed.

Claims 1-26 meet the criteria under PCT Article 33(4) because the presently claimed methods of treating radiation induced enteritis would each have applicability in the medical industry, particularly for ameliorating the symptoms associated with such a condition and in order to improve the quality of life of patients suffering from such a condition.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing, the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.